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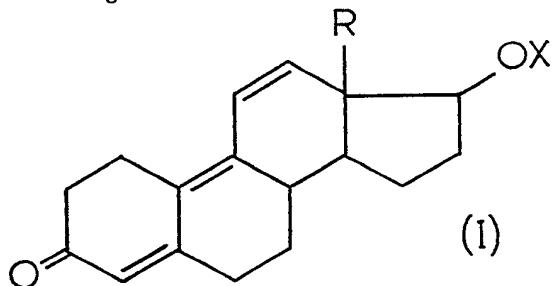
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(54) **Zootechnic and/or veterinary compositions**

(57) The present invention provides zootechnic and/or veterinary compositions which afford excellent results with the growth of pigs, in particular with respect to gain in weight.

The compositions of the invention comprise from 10 to 50 mg of zeranol and from 5 to 50 mg of a steroid of the general formula:



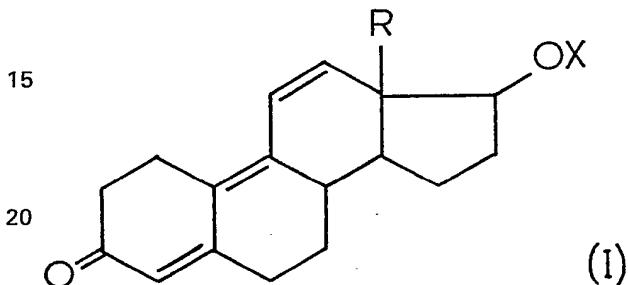
wherein R represents an alkyl radical of from 1 to 3 carbon atoms and X represents a hydrogen atom, an acyl radical of from 1 to 18 carbon atoms, a saturated or unsaturated hydrocarbyl radical of from 1 to 6 carbon atoms, or a saturated or unsaturated hydrocarboxyhydrocarbyl radical of from 2 to 5 carbon atoms.

## SPECIFICATION

## Zootechnic and/or veterinary compositions

5 The present invention relates to zootechnic and/or veterinary compositions, and in particular to compositions containing zeranol and a steroid.

In our co-pending Application No. 16,685/78 (Serial No. 1,597,619) there are described and claimed 10 zootechnic and/or veterinary compositions comprising zeranol and a steroid of the general formula:



25 wherein R represents an alkyl radical containing from 1 to 3 carbon atoms and X represents a hydrogen atom, an acyl radical of from 1 to 18 carbon atoms, a saturated or unsaturated hydrocarbyl radical of from 1 to 6 carbon atoms or a saturated or 30 unsaturated hydrocarboxyhydrocarbyl radical of from 2 to 5 carbon atoms, optionally together with one or more substances included to improve the reabsorption characteristics of the compositions, in particular an anti-inflammatory compound.

35 The above compositions are intended to promote an increase in weight in stock animals such as cattle and pigs. The simultaneous presence of two active agents reinforces in an unexpected manner the favourable action on the growth of the animals of 40 each of the active agents such that the resulting increase in weight is considerably greater than that which might have been expected, taking account of the known properties of each active agent.

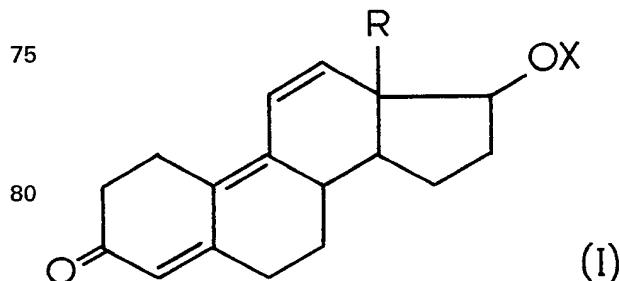
For cattle, and especially bullocks, the earlier disclosure indicates that such compositions advantageously contain from 10 to 100 mg and, preferably, from 20 to 60 mg of zeranol and from 50 to 400 mg, and preferably from 100 to 300 mg, of a steroid of 50 formula I. For their administration to livestock, the above compositions can be deposited in the form of an implant in the dermis, preferably at the base of the ear. The implant is preferably deposited in cattle, for example, from 20 days to 4 months, and more preferably from 1 to 3 months, before slaughter.

55 Application No. 16,685/78 describes in a general way all combinations containing zeranol and a steroid of formula I, and while it does also describe in a more particular manner the combinations mentioned above, the earlier Application basically is concerned in its more particular aspects with compositions containing a much greater quantity of a steroid of the formula I than of zeranol.

We have now found surprisingly that excellent results with the growth of pigs can be obtained, in 65 particular with respect to gain in weight, by adminis-

tering to pigs a composition in which the amount of steroid of formula I is less than that proposed earlier.

Accordingly, the present invention provides zootechnic and/or veterinary compositions, which 70 compositions comprise from 10 to 50 mg, of zeranol and from 5 to 50 mg, preferably 5 to less than 50 mg, of a steroid of the general formula:



85 wherein R represents an alkyl radical of from 1 to 3 carbon atoms and X represents a hydrogen atom, an acyl radical of from 1 to 18 carbon atoms, a saturated or unsaturated hydrocarbyl radical of from 1 to 6 carbon atoms, or a saturated or unsaturated hydrocarboxyhydrocarbyl radical of from 2 to 5 carbon atoms, that is a radical in which one of the carbon atoms of a saturated or unsaturated hydrocarbyl radical of from 1 to 6 carbon atoms is replaced by an oxygen atom.

90 In the steroids of general formula I, when X represents a saturated hydrocarbyl radical this may be a methyl, ethyl, propyl, *isopropyl*, butyl or *isobutyl* radical. When X represents an unsaturated hydrocarbyl radical this may be an alkenyl or an alkynyl radical; and the preferred alkenyl radical is a 2-methyl-allyl or 3-methyl-2-but enyl radical.

When X represents a hydrocarboxyhydrocarbyl radical this may be saturated or unsaturated and a preferred radical is the methoxymethyl radical.

105 As an acyl radical, X is preferably derived from an alcanoic acid such as acetic, propionic, butyric, *isobutyric* or undecylic acid, from a cycloalkylcarboxylic or cycloalkylalkanoic acid such as cyclopropyl-, cyclopentyl- or cyclohexylcarboxylic acid, cyclopropyl-, cyclopentyl- or cyclohexylacetic acid or cyclopropyl-, cyclopentyl- or cyclohexylpropionic acid, from an aromatic acid such as benzoic, phenylacetic or phenylpropionic acid or from formic acid.

115 Preferred compositions according to the invention are those which contain a steroid of formula I in which R represents a methyl radical, and those which contain a steroid of formula I in which X represents an acyl radical of from 1 to 18 carbon atoms.

120 More preferably the compositions of the invention are those wherein the steroid of formula I is 3 - oxo - 17 $\beta$  - acetoxy - estra - 4,9,11 - triene.

Preferably also the compositions of the invention are compositions which contain from 10 to 40 mg of

125 zeranol, together with from 10 to 30 mg of 3 - oxo - 17 $\beta$  - acetoxy - estra - 4,9,11 - triene. In particular, the compositions are most preferably those that contain from 10 to 40 mg of zeranol and 20 mg of 3 - oxo - 17 $\beta$  - acetoxy - estra - 4,9,11 - triene.

130 As has been pointed out above, the compositions

of the invention enable very good results to be obtained with pigs. Thus the compositions of the invention preferably are such as may be administered to pigs.

5 It is to be understood, however, that the compositions of the invention are not limited to those that can only be administered to pigs; the compositions of the invention in their broadest use aspect can also be administered, for example, to cattle, sheep and  
10 poultry.

The compositions of the invention are preferably administered in the form of implants. These implants may be placed in the neck of the animal or in the buttock muscles and are implanted, for example, from 20 days to 4 months, preferably from 1 to 3  
15 months, before slaughter.

The compositions according to the invention also may be administered by injection, and for that purpose may be in the form of solutions or suspensions,  
20 or they may be administered orally. Implants, however, offer the advantage of being better resorbed.

The compositions of the invention also exhibit useful pharmacological properties, in particular anabolizing properties and, more particularly, proteinic anabolizing properties. These properties make the compositions according to the invention suitable for use also as veterinary medicaments, particularly for augmenting a general organic resistance to attacks of all kinds, combating retardation of growth,  
25 emaciation, general organic troubles connected with old age, and equally for combating in a secondary manner infectious, parasitic and nutritional diseases.

In veterinary use the compositions of the invention may be mixed with other ingredients of veterinary  
30 compositions as known *per se*, the content of active principles of the composition according to the invention in the overall formulation varying according to the animal species.

For example, other active materials may be incorporated in the compositions of the invention for the purpose of increasing resorption of the compositions. Amongst these active materials, and particularly useful for compositions intended for implantation, are anti-inflammatory compounds and preferentially steroids of the cortisone type.

The expression "steroids of the cortisone type" is used herein to mean a steroid having anti-inflammatory properties similar to cortisone and bearing a ketone function at the 3 position of the steroid nucleus, a hydroxy group or a ketone function at the 11 position, a free or esterified ketol chain at the 17 $\beta$  position and a hydrogen atom or a hydroxy group at the 17 $\alpha$  position, with either one or two double bonds in the A ring; the steroid nucleus  
50 may also bear other substituents such as a chlorine or fluorine atom at the 4 position, a methyl or a trifluoromethyl group or a halogen atom such as fluorine at the 6 position, a halogen atom such as fluorine at the 9 position, a methyl group at the 16 $\alpha$  or 16 $\beta$  position or a methylene group at the 16 position, and a methylene or difluoromethylene bridge between the 6 and 7 positions.

The preferred steroid of the cortisone type for inclusion in the compositions of the invention is  
65 dexamethasone - ( $\beta$ -ethoxy -  $\beta$ -ethoxy) - ethoxy -

acetate.

The compositions of the invention may preferably contain from 0.05 to 5 mg of a steroid of the cortisone type.

70 In some circumstances, it may be desirable for the compositions of the invention to include a suitable vehicle. The term "suitable vehicle" is used herein to exclude any possibility that the nature of the vehicle could be harmful to the animal being treated. The choice of vehicle will of course also be determined by the route by which it is intended to administer the composition, and it is believed to be within the competence of those accustomed to the preparation of formulations of this type to make such a choice.

75 Preferred vehicles for use in the compositions of this invention are:-  
a) the excipient of a tablet, pellet, implant or pill;  
b) a sterile injectable liquid solution or suspension medium.

80 The compounds utilized in the compositions according to the invention are known *per se*; zeronol or zearalanol (see Merck Index 1976, 9th edition 9781) can be prepared, for example, according to the process described in U.S. Patent Specification No.  
90 3,239,345.

85 Compounds of formula I can be prepared according to processes described in French Patent Specifications Nos. 1,380,414 and 1,492,985, as well as in Belgian Patent Specification No. 696,084.

95 The invention also includes a method of animal husbandry, which method comprises rearing one or more animals to achieve an increase in weight and thereafter slaughtering the animals, the method including the step of administering to the animals a composition according to the invention.

100 The following examples illustrate the invention, without, however, limiting it:

*Example 1: Zootechnic composition in the form of an implant.*

105 An implant was prepared containing:  
zeranol 36 mg  
3-oxo 17 $\beta$ -acetoxy estra 4,9,11-triene 20 mg

*Example 2: Zootechnic composition in the form of an implant.*

110 An implant was prepared containing:  
zeranol 24 mg  
3-oxo 17 $\beta$ -acetoxy estra 4,9,11-triene 20 mg

*Example 3: Zootechnic composition in the form of an implant.*

115 An implant was prepared containing:  
zeranol 12 mg  
3-oxo 17 $\beta$ -acetoxy estra 3,9,11-triene 20 mg

*Example 4: Comparison of effects on animals of various zootechnic compositions.*

120 This test was carried out on castrated male Large-White-Landrace pigs. The animals were fattened in industrial-type piggeries and housed in enclosures able to contain 7 to 10 pigs. The animals were divided into 4 groups:

- 125 one control group;  
one group to which the implant of Example 1 was administered;  
one group to which the implant of Example 2 was administered; and  
130 one group to which the implant of Example 3 was

administered.

The implants were introduced into the subcutaneous tissue behind the ear, 63 days before

slaughter. All the animals received the same foods-  
5 tuff and the results obtained are set out in Table 1  
below:

Table 1

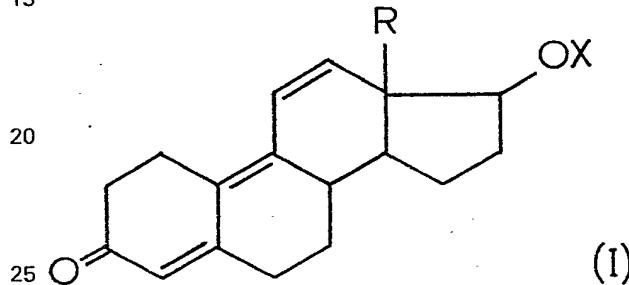
Treatment	Controls	Animals		
		Those having received the implant of Example		
		1	2	3
Period in days before slaughter	63	63	63	63
Group No.	1	2	3	4
Number of animals	15	14	15	14
Number of days of fattening	63	63	63	63
Mean weight on day of treatment (Kg)	65.53	65.07	64.67	65.00
Mean weight at the end of the test (Kg)	101.40	102.79	106.13	102.36
Mean gain in weight (Kg)	35.87	37.72	41.46	37.36
Mean daily gain in weight (Kg)	0.569	0.599	0.658	0.593

As can be seen from Table 1 the compositions of Examples 1, 2 and 3 enable the daily gain in weight to be very clearly improved.

#### 10 CLAIMS

1. A zootechnic and/or veterinary composition, which composition comprises from 10 to 50 mg of zeranol and from 5 to 50 mg of a compound of the formula:

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wherein R represents an alkyl radical of from 1 to 3 carbon atoms and X represents a hydrogen atom, an acyl radical of from 1 to 18 carbon atoms, a saturated or unsaturated hydrocarbyl radical of from 1 to 6 carbon atoms or a saturated or unsaturated hydrocarboxyhydrocarbyl radical of from 2 to 5 carbon atoms.

2. A composition according to claim 1, wherein the compound of formula I is one in which R represents a methyl radical.

3. A composition according to claim 1 or claim 2, wherein the compound of formula I is one in which X represents an acyl radical of from 1 to 18 carbon atoms.

4. A composition according to claim 3, wherein the compound of the formula I is 3 - oxo - 17 $\beta$ -

acetoxy - estra - 4,9,11 - triene.

5. A composition according to any one of the preceding claims, which contains from 10 to 40 mg of zeranol and from 10 to 30 mg of 3 - oxo - 17 $\beta$ -acetoxy - estra - 4,9,11 - triene.

6. A composition according to claim 5, which contains from 10 to 40 mg of zeranol and 20 mg of 3 - oxo - 17 $\beta$  - acetoxy - estra - 4,9,11 - triene.

7. A composition as claimed in any of the preceding claims which also contains an anti-inflammatory compound.

8. A composition as claimed in claim 7, in which the anti-inflammatory compound is a steroid of the cortisone type as hereinbefore defined.

9. A composition as claimed in claim 8, in which the steroid of the cortisone type is dexamethasone - ( $\beta$  - ethoxy -  $\beta$  - ethoxy) - ethoxy acetate.

10. A composition as claimed in claim 8 or claim 9 and containing 0.05 to 5 mg of the steroid of the cortisone type.

11. A composition according to any one of the preceding claims which also includes a suitable vehicle.

12. A zootechnic and/or veterinary composition substantially as hereinbefore described in any one of specific Examples 1 to 3.

13. A method of animal husbandry, which method comprises rearing one or more animals to achieve an increase in weight and thereafter slaughtering the animals, the method including the step of administering to the animals a composition according to any one of the preceding claims.

14. A method according to claim 13, wherein the animals reared are pigs.

15. A method according to claim 13, wherein the animals reared are cattle, sheep or poultry.

16. A method according to any one of claims 13 to 15, wherein the composition is administered as an implant.

17. A method according to claim 16, wherein the 5 implant is placed in the neck of the animal or in the buttock muscles.

18. A method according to claim 16 or claim 17, wherein implantation is effected at a time from 20 days to 4 months before slaughter.

10 19. A method according to claim 18, wherein implantation is effected at a time from 1 to 3 months before slaughter.

20. A method according to claim 13 substantially as hereinbefore described specifically.

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